instruments to their own use. Two techniques were especially successful in opening up the territory between biochemistry and cytology to exploration: (a) obtaining micrographs showing the fine structure of cells using the electron microscope; and (b) chemical analysis of cell fractions separated by means of the ultracentrifuge. This chapter will focus on development of these techniques in the 1940s and 1950s, focusing on the epistemic issues raised by their introduction (beyond those that had already been resolved in the fields in which the instruments had been developed). The surge of discoveries and new understandings of cell mechanisms made possible by these new instruments and techniques will then be the focus of Chapters 5 and 6.[3]

1. THE EPISTEMOLOGY OF EVIDENCE: JUDGING ARTIFACTS

I used a compelling visual illusion to demonstrate that the concern with artifacts arises even before we turn to the use of instruments to procure evidence in science. The problem is much accentuated when instruments and the techniques for using them require manipulating and altering the phenomenon under investigation. Sometimes, as amply illustrated in cell fractionation, the manipulations and alterations are severe. A major goal of cell fractionation is to pinpoint the particular organelle in which each enzyme is found and, therefore, determine the biochemical reaction associated with the organelle. Using cell fractionation to pursue this goal requires radically disrupting the cell. Force is applied to break its tough plasma membrane, and the contents are dispersed into a medium different from that in living cells. The contents are then subjected to forces several thousand times that of gravity in the centrifuge. The underlying assumption is that different cell constituents will settle in order of their mass, with the components of greatest mass settling first. Typically, the process involves several iterations in which the contents may be resolubilized in yet different media and subjected again to centrifugation. (Figure 4.3 in Section 2 illustrates a common version of the procedure.) Each iteration generates what is called a *fraction* of the original material that is then assayed for the reactions it supports and hence what enzymes it contains.

[3] Additional instruments and techniques that will be important at various points in the historical analysis that follows include techniques of histochemistry and cytochemistry, which used various stains to detect the location and sometimes quantify the amounts of DNA, RNA, and certain enzymes; the use of radioactive tracers to follow the migration of substances through the cell; various forms of spectroscopy that enabled the detection of reaction products; and several new types of microscopes, including phase contrast and fluorescent microscopes. A number of investigators also explored techniques for micromanipulation or microsurgery, which allowed them to dissect parts of cells, remove parts, and inject substances into them.